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Paper No: 31
Appeal No: 2003-0337
Appellant: SUMMERS NEENA L.
Application: 08/954,954

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Board of Patent Appeals and Interferences
Docketing Notice

Application 08/954,954 was received from the Technology Center at the Board on November 6, 2002 and has been assigned Appeal No: 2003-0337.

A review of the file indicates that the following documents have been filed by appellant:

Appeal Brief filed on:	January 3, 2002
Reply Brief filed on:	None
Request for Hearing filed on:	January 3, 2002

In all future communications regarding this appeal, please include both the application number and the appeal number.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 29

Application Number: 08/954,954
Filing Date: 21 October 1997
Appellant(s): SUMMERS ET AL.

S. Christopher Bauer
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 03 January 2002 (Paper No. 28).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

It is noted that Appellant appears not to have received the Advisory Action mailed to G.D. Searle and Co., Corporate Patent Law Department, on 23 May 2001 (Paper No. 25). A copy of the advisory action is attached.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that all of the appealed claims do not stand or fall together, although no substantive reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8) have been provided.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,635,599	***Pastan et al.***	***6-1997***
4,703,008	***Lin***	***10-1987***
4,751,180	***Cousens et al.***	***6-1988***

Chaudhary et al., 1989, Nature 399:394-397.

WO 94/24160, Brigham and Women's Hospital, 27 October 1994

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. (U.S. Patent 5,635,599) in view of Lin (U.S. Patent 4,703,008).

Pastan et al. teach growth factor receptor agonist polypeptides and nucleic acids encoding same, comprising a modified growth factor amino acid sequence, wherein the modification comprises the linear rearrangement wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini in the middle of the polypeptide (Fig. 1; column 2, brief description of Fig. 1; column 3, lines 35-53). Pastan et al. teach that erythropoietin (EPO) is amenable to this procedure, which they term "circular permutation" (column 4, lines 30-42). Preferred linkers are discussed at column 7, as including GGNGG, and GGGNGGG. Pastan et al. teach a method of recombinantly producing the circularly permuted ligand (column 9, line 62 to column 10, line 15). Pastan et al. also teach pharmaceutical compositions comprising the circularly permuted growth factor, complementary growth factors, and a pharmaceutically acceptable carrier (columns 16-17). Pastan et al. disclose other hematopoietic growth factors, including GM-CSF, G-CSF, M-CSF, IL-1, IL-2, IL-3, IL-4, IL-6 and IL-7 (col. 5, lines 27-44).

Pastan et al. do not disclose a working example of circularly permuted EPO, nor do they disclose a sequence of EPO. However, human EPO had been previously characterized (Lin; Figure 9). Pastan et al. disclose that a good choice for an "opening site" (i.e., a new C- and N-termini) is at a site that is tolerant to amino acid substitution or in a region of the protein that does not show highly conserved sequence identity between closely related proteins in an alignment (column 8, lines 30-54). Lin in Figure 9 align human and monkey EPO sequences. Both are functional. Differences occur at

amino acid positions 25, 27, 30, 32, 80, 82, 88, 116, and 121. This suggests that an opening site would be tolerated in a circularly permuted EPO molecule at any one of these sites. Lin also teach pharmaceutical composition comprising EPO and a pharmaceutically acceptable carrier, and a method of stimulating the production of hematopoietic cells in a patient comprising administration of same (column 12). Note that EPO stimulates erythropoiesis, the production of red blood cells, a form of hematopoiesis (col. 5, lines 52-60).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the circularly permuted growth factors, DNA encoding same, methods of recombinantly producing same, pharmaceutical compositions comprising same and methods of administering same as taught by Pastan et al., and to modify that teaching by extending it to EPO disclosed by Lin, with opening sites at 25, 27, 30, 32, 80, 82, 88, 116, or 121. A reasonable expectation of success is given by Pastan et al.'s disclosure that preferred opening sites are those which can tolerate amino acid substitution and Lin's disclosure of substitution toleration at positions 25, 27, 30, 32, 80, 82, 88, 116, and 121. The motivation to do so is provided by Pastan et al. in their express suggestion to extend the teachings to EPO.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

Claims 1-4 and 6-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin as applied to claims 1, 5 and 10-14 above, and further in

view of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

Pastan et al. in view of Lin teach circular permuteins of EPO embraced by claim 1, for example. Neither reference teaches the specific GlySer-rich linker sequences as required by claims 2-4 and 6-9.

Chaudhary et al. disclose the use of a 45 base pair linker for connecting two antibody variable domains in a fusion protein. The linker encoded a 15 residue long stretch of Gly and Ser residues, see Fig. 1a. Cousens et al., disclose that non-polar amino acids such as Gly and Ser are useful for a flexible linker (column 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the circular permuteins of EPO as taught by Pastan et al. in view of Lin, and to modify that combined teaching by using GlySer-rich flexible linkers between the two portions of the circular permuteins as taught by Chaudhary et al. and Cousens et al. with a reasonable expectation at successfully achieving a circular permutein with sufficient flexibility in the linker for the two portions of the circular permutein to fold favorably for retained function. The motivation to do so is provided by the disclosures of Chaudhary et al. and Cousens et al. which disclose that the flexible linkers do not destroy activity.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

(11) Response to Argument

(A) Issue 1 - Whether claims 1, 5 and 10-14 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008)

Beginning at p. 7, Appellant argues that the prior art merely invites further experimentation, and that the instant rejection is improperly based on an "obvious to try" standard. Appellant characterizes Pastan et al. as being limited to two working examples disclosing only two circular permutation breakpoints of IL-4 and these molecules in the context of a chimeric molecule with a cytotoxin or an antibody fragment. Appellant urges that only prophetic examples are disclosed regarding IL-2, G-CSF and GM-CSF, and that it is not shown that those molecules folded properly or had any activity. This has been fully considered but is not found to be persuasive. Appellant is reading Pastan et al.'s disclosure too narrowly. Not only did Pastan et al. disclose that circular permutation could result in active variants, they also provided guidance regarding selection of opening sites and the routine nature of making circular permuteins and screening for active variants. Importantly, Pastan et al. has claims to permuteins of IL-2, GM-CSF and G-CSF in spite of there being only prophetic examples pertaining to these. In view of Pastan et al., no rejection of the instant claims was made under 35 U.S.C. § 112, first paragraph, regarding the scope of the permutated erythropoietin receptor agonist protein, despite the enormous breadth of the instant claims. Claim 1 recites 67 opening sites occurring across the length of erythropoietin, and these opening sites could occur in any one of several deletion mutants of

erythropoietin. Importantly, none of the claimed proteins were tested for activity in the instant application.

Beginning at p. 8 of the Brief, Appellant argues that Pastan et al. provides only general guidance regarding opening sites in a protein and only provides two operational breakpoints for IL-4. Appellant characterizes Pastan et al. as providing a general approach, a series of options, and suggesting trying each of the options until one possibly arrives at a successful result. Appellant urges that case law sets forth that the prior art must set forth what the critical parameters are. Appellant characterizes Pastan et al. as failing to provide the critical parameters for erythropoietin (EPO). Appellant argues that the references must provide an enabling disclosure; that if a reference discloses only a hypothetical chemical structure and does not enable production, the references do not raise a question of obviousness. Appellant urges that the instant situation is analogous. This has been fully considered but is not found to be persuasive. Pastan et al. is a U.S. Patent. A patent is presumed valid unless proven otherwise in a court of law. The claims of Pastan et al. are broad, allowing for an opening site anywhere in any one of four molecules (IL-4, IL-2, GM-CSF and G-CSF) as long as the resulting circular permutein retains activity. Such was deemed enabled by Pastan et al.'s disclosure. Furthermore, contrary to Appellant's position, Pastan et al. provide the critical parameters regarding choice of opening sites. Pastan et al.'s discussions regarding substitution tolerance, and secondary and tertiary structure provide detailed guidance regarding how to choose an opening site in any soluble protein such as a growth factor (see col. 7-9). While it is true that Pastan et al. do not suggest specific

opening sites for EPO, they do suggest extending the teachings of the specification to EPO. However, EPO was well characterized as of Appellant's filing date. Lin provides detailed structural analysis of EPO, including the sort of substitution tolerance analysis deemed critical by Pastan et al., such that one of ordinary skill in this art would have been motivated to choose one of the many opening sites recited in the instant claims with a reasonable expectation of success. The motivation and reasonable expectation of success were addressed in the 103 rejection set forth above. Again, Appellant appears to be holding Pastan et al. to a higher standard than that achieved by the instant application, wherein the instant application provides no working examples. Also, the instant application does not provide more guidance regarding selection of opening sites than Pastan et al. (see specification, pages 25-27).

Beginning at p. 9, Appellant argues that there are further fatal errors in the *prima facie* case of obviousness. Appellant argues that Lin does not teach individual sites at which amino acid substitutions could be made, based on an alignment of human and monkey EPO. Appellant urges that, at best, all of the fourteen differences between human and monkey EPO would be required for an active EPO protein, and that there is no support in Lin that only one could be made without loss of activity. This is not found to be persuasive, because it is not sound scientific reasoning that all of the positions must be substituted for retained activity. Artificially generated muteins having fewer substitutions are common. Lin discloses at column 11 that synthetic sequences that are partially duplicative of any of the two naturally occurring sequences could be made which retain activity. The disclosure of the alignment provides the skilled artisan with

guidance as to which residues are not absolutely conserved. These would be good candidates for substitution. Regarding the disclosure of Lin regarding other substitution-tolerant sites which are not taught as appropriate breakpoints in the instant disclosure, it is not required that Pastan et al. in view of Lin point to only those points that would absolutely result in active circular permuteins. All that is required is a reasonable expectation of success. Lin points to several substitution-tolerant residues. Pastan et al. teach that such are good *candidates* for breakpoint introduction. It would have been routine to screen for those breakpoints that resulted in active circular permuteins. It is important to remember that the claimed invention lists any of 67 potential breakpoints, in any one of four EPO sequence variants, none of which have been exemplified in the specification. Surely, the claims embrace inoperative embodiments. However, this is legally permissible, since there would only be a reasonable number of inoperative embodiments, and the screening assay is disclosed such that the active permuteins could easily have been identified by the ordinary skilled artisan.

Beginning at p. 10 of the Brief, Appellant reviews the findings of the court in *In re Amgen*, cited in the Brief, which ruled on the Lin et al. patent 4,703,008 applied in the instant rejection. Appellant points to the court's ruling that the '008 patent's specification does not provide enabling support for claims embracing biologically functional EPO gene analogs. Appellant concludes that '008 can only be relied upon for enabling the sequences of monkey and human EPO, but not analogs thereof such as amino acid sequences having substitutions at which murine and human EPO differ. This has been fully considered but is not found to be persuasive. First, it appears that Appellant may

have cited the incorrect case, as *In re Amgen* does not appear in the USPQ at the indicated pages. Rather, it appears that Appellant may have intended *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ2d 1016), which ruled on the Lin et al. patent 4,703,008 applied in the instant rejection. However, the instant fact pattern is clearly distinguished from the fact pattern used in the *Amgen v. Chugai* decision. In *Amgen v. Chugai*, the court was determining enablement issues relevant to gene sequences, not amino acid sequences. Moreover, in the instant rejection, '008 is not relied upon for teaching *any* biologically functional analog. Rather, Pastan et al. (5,635,599) is being relied upon for teaching circular permutation of soluble ligands or growth factors, for suggesting EPO as such a growth factor (column 4, line 40), and for suggesting that non-conserved amino acid positions in an alignment of two closely related proteins are good candidates for opening sites (column 8, lines 45-53). '008 provides the alignment of two closely related EPO proteins, one from human and the other from monkey, and shows which amino acid residues are non-conserved, which is exactly what Pastan et al. suggest. Following the disclosure of Pastan et al. ('599), these are good candidates for opening sites, and provide a reasonable expectation of success. Pastan et al. ('599) also teach how to confirm that these are good opening sites, by making the circular permuteins and testing for native activity. Therefore, the combined teachings suggest the claimed invention with a reasonable expectation of success.

Beginning at p. 10 of the Brief, Appellant argues that the comparison of two sequences is too narrow. Appellant points to WO 94/24160 (of record) as providing an alignment of more EPO sequences. Appellant argues that, of the fourteen non-

conserved residues between human and monkey EPO, one or the other of the amino acids of human or monkey are conserved in multiple other species. Appellant also points to 47 additional positions which are non-conserved between the seven species, and thus there is no clear teaching as to which position is suitable for a breakpoint. This argument is not found to be persuasive. The instant claims recite any one or 67 opening sites, many of which occur at the specific sites criticized by Appellant. The alignment of two molecules disclosed by Lin provide enough information to choose several potential breakpoints that are tolerant to substitution. These could have been easily tested for activity by the ordinary skilled artisan at the time of the invention. There was a reasonable expectation of success to arrive at at least one of the 67 permuteins of any of 4 EPO sequence variants recited in the claims.

Beginning at p. 11 of the Brief, Appellant argues that Pastan et al.'s suggestions regarding choice of a breakpoint (or opening site) are inconsistent. Appellant refers to glycosylation sites, non-conserved positions, non-structured regions, substitution-tolerant sites are all suggested as good breakpoints by Pastan et al. However, Appellant is concerned that some sites in EPO are conserved *and* tolerant to substitution, or are a glycosylation site *and* conserved. Thus, Appellant queries which of Pastan et al.'s suggestions are correct. This is not found to be persuasive. Pastan et al. never state that a potential breakpoint site must meet *all* of the criteria. Pastan et al. provide detailed guidance to the ordinary skill artisan to choose a breakpoint and screen the resulting permutein *with a reasonable expectation to successfully obtain an active permutein*. Such screening was considered routine. Again, Appellant is demanding

much more of Pastan et al.'s disclosure than is given in the instant specification, especially considering the enormous breadth of the instant claims, and the lack of working examples of any of the claimed proteins.

Beginning at the bottom of p. 11 of the Brief, Appellant lists other alleged deficiencies of the obviousness rejection of record. First, Appellant points to specific teachings of Pastan et al. that the termini of the protein to be permuted must have termini that are in close proximity and favorably located, and that the opening site should be chosen such that new termini can be formed without disrupting a region critical for protein folding or final protein configuration. Appellant characterizes the prior art as establishing the unpredictability of whether the permutated protein will fold. Appellant concludes that the cited prior art fails to provide guidance regarding the critical elements of EPO termini proximity, crucial regions for the folding process or final conformation/activity. This is not found to be persuasive. Pastan et al. specifically state that "because the linker may be of any length, close proximity of the native termini is not an absolute requirement" (col. 7, li. 29-31). Pastan et al. provide more guidance on this subject when they state "it is desirable to use a linker that preserves the spacing between the termini comparable to the unpermuted or native molecule" (col. 7, li. 32-34). Moreover, Pastan et al. provide specific guidance regarding selection of breakpoints and suggests screening for activity, and Lin provides a routine EPO activity assay. This guidance and the routine nature of screening for active permuteins earned Pastan et al. their broad claims, and is the reason why no enablement rejection was

made against the instant claims, despite the fact that the instant claims are extremely broad.

Beginning at p. 13 of the Brief, Appellant argues that the prior art shows that the results of circular permutation have been highly variable. Appellant points to examples including dihydrofolate reductase, ribonuclease T1, omp A, and yeast phosphoglycerate dehydrogenase circular permuteins with lowered activity, solubility or thermodynamic stability. Appellant takes issue with the Examiner's characterization of Pastan et al. as a pioneering patent and urges that there is no objective legal test for such. Appellant also stresses that circular permutation was known as far back as 1983, and that a general method of circular permutation was disclosed in 1992. This is not found to be persuasive. The prior art examples pointed to by Appellant mostly pertain to enzymes (not soluble growth factors, which are at issue here) wherein a single opening site was evaluated. Pastan et al. were the first to establish that circular permuteins of soluble proteins (such as soluble EPO) could be circularly permuted at a number of sites along the length of the protein and retain activity. Pastan et al. were also the first to provide guidance regarding choice of opening sites. Appellant has repeatedly been advised that their position regarding the unpredictable nature of the results of making circular permuteins are inconsistent with the scope of their claims, and the lack of data disclosed in their specification. Appellant has also bee advised that evidence of unexpected results, such as evidence demonstrating that a particular claimed species has a particular activity, would have been given considerable weight in overcoming this

rejection. However, no such evidence has been brought forward in the prosecution history of the instant application.

At p. 14 of the Brief, Appellant argues that the rejection is improperly based on the existence of a general method of making circular permuteins (Pastan et al.), which is irrelevant as to the question of whether the specific molecules would have been obvious. Appellant is incorrect with respect to the facts. Pastan et al. provide numerous examples of circular permuteins of a soluble ligand. Lin provides the motivation and reasonable expectation of success to generate specific circular permuteins of EPO, based on Pastan et al.'s specific suggestion to extend their teachings to EPO. Furthermore, the fact patterns in *In re Bell* and *In re Deuel*, cited by Appellant in support of their argument, are considerably different than the fact pattern here. In *Bell* and *Deuel*, the issue was whether or not a gene was obvious from a prior art's disclosure of a protein sequence and general gene isolation methods. In the instant case, the prior art teaches a circularly permuted growth factor receptor agonist, the full sequence of the EPO growth factor, and guidance regarding appropriate breakpoints in EPO that are also recited in the claims.

Beginning at p. 15, Appellant reviews the prosecution history of Pastan et al. Appellant stresses that an enablement rejection regarding the scope of the permuteins was withdrawn in Pastan et al.'s prosecution history without explanation. Appellant urges that the file history clearly established the lack of enablement beyond what was claimed. The Examiner maintains that it is improper to review the file history of Pastan et al. on this record. The fact remains that the claims of Pastan et al. are broadly drawn

to circular permuteins of any one of four proteins with numerous opening sites, and that a patent is considered valid (including fully enabled) unless proven otherwise in a court of law. Furthermore, the specification of Pastan et al. provides guidance regarding the critical parameters that must be considered when choosing an opening site, and furthermore that screening for active permuteins is routine. Lin provides the structural and functional analysis of EPO that motivate the ordinary skilled artisan to select an opening site, including at least one from the many species recited in the instant claims, with a reasonable expectation of success.

(B) Issue 2 - Whether claims 1-4 and 6-9 are patentable under 35 U.S.C. § 103(a), over Pastan et al. (U.S. Patent 5,635,599) taken in view of Lin (U.S. 4,703,008), Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S> Patent 4,751,180)

At p. 15 of the Brief, Appellant argues that the linkers of Chaudhary et al. and Cousens et al. are in the context of fusion proteins, and the requirements for joining fusion proteins are different from the requirements for joining the ends of circular permuted molecules. Appellant characterizes the prior art as teaching that a linker can act as a hinge to further separate the two fused polypeptides and provide for steric flexibility. Appellant contrasts this with a linker that allows for intermolecular interaction in a circular permutein. Appellant points out that Pastan et al. distinguish between the two by calling one a linker and the other a spacer. This is not found to be persuasive. Pastan et al. teach preferred linkers within circular permuteins at column 7, as including

GGNGG, and GGGNGGG. Chaudhary et al. and Cousens et al. teach that similarly structured linkers could have been easily generated, and that activity of the proteins in which the linkers are used could have been routinely screened.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Elizabeth C. Kemmerer

ECK
February 8, 2002

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